A phase 1 trial to assess P-gp mediated drug interactions with ASTX660 in healthy volunteers

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Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON50115

Source
ToetsingOnline

Brief title
ASTX660 P-gp interaction study

Condition

- Leukaemias

Synonym
acute myeloid leukemia, advanced solid tumors, lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Astex Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Ministerie van OC&W,Pharmaceutical Industry

Intervention

Keyword: ASXT660, P-gp

Outcome measures

Primary outcome

- To determine the effect of P-glycoprotein (P-gp) inhibition by quinidine on

pharmacokinetics (PK) of ASTX660

- To determine the effect of P-gp inhibition by ASTX660 on PK of fexofenadine

Secondary outcome

- To determine the safety and tolerability of ASTX660 following oral

administration alone or in combination with quinidine, a P-gp probe inhibitor;

or with fexofenadine, a P-gp probe substrate

Study description

Background summary

ASTX660 is a new compound that may potentially be used for the treatment of patients with advanced solid tumors, lymphoma, and acute myeloid leukemia (AML, cancer of blood and bone marrow) and for whom standard life prolonging measures are not available.

Study objective

The main purpose of this study is to investigate the effect of ASTX660 on how quickly and to what extent quinidine and fexofenadine are absorbed, distributed, broken down and eliminated from the body.

Quinidine and fexofenadine have been chosen because they are known to interact with a certain enzyme in the liver. By looking at the effect of ASTX660 on these agents, something can also be said about whether ASTX660 has an influence on this enzyme. This is important to know when ASTX660 is given in the future along with agents that are also interacting with this enzyme.

The safety of ASTX660 as well as how it is tolerated in the presence of

quinidine and fexofenadine will also be investigated.

We also look at the effect of the genetic information on the body*s response to ASTX660. This part of the study is mandatory.

ASTX660 has been used by humans before. In addition, it has been extensively tested in the laboratory and on animals. Quinidine and fexofenadine are already available on the market in several dosages and formulations for the treatment of cardiac arrythmias (quindine) and allergies such as hay fever (fexofenadine).

Study design

For the study it is necessary that the volunteers stays in the research center for 2 periods of 4 days (3 nights). There will be an in between period of at least 7 days between the administration of the study compound in Period 1 and the administration of the study compound in Period 2.

Day 1 is the day when the volunteer receives the study compound. In each period, the volunteer is expected at the research center the day before the day of first administration of the study compound. The volunteer has to be at the research center at 14:00 hrs in the afternoon. The volunteer will leave the research center on Day 3 of each period.

Intervention

During the study the volunteer will receive ASTX660, quinidine (Group 1 only), or fexofenadine (Group 2 only) after an overnight fast (at least 10 hours).

The volunteer will be given ASTX660, quinidine (Group 1 only), or fexofenadine (Group 2 only) as oral capsules (ASTX660) or tablets (quinidine or fexofenadine) with 240 milliliters (mL) of (tap) water.

During each treatment period the volunteer will continue fasting until 4 hours after administration of the study compound. Then he/she will receive lunch. During fasting the volunteer is allowed to drink water with the exception of 2 hours prior to until 1 hour after administration of the study compound.

During the first 4 hours after administration of the study compound the volunteer will not be allowed to lie down (except when instructed to do so by one of the investigators), as this may influence the uptake of the study compound.

The study consists of 2 treatment periods. In Group 1, the volunteer will receive ASTX660 (120 mg) alone on the first day of Treatment Period 1 and ASTX660 (120 mg) and quinidine (600 mg) at the same time on the first day of

Treatment Period 2. In Group 2, the volunteer will receive fexofenadine (120 mg) alone on the first day of Treatment Period 1 and fexofenadine (120 mg) with ASTX660 (180 mg) at the same time on the first day of Treatment Period 2.

Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, sweating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about 270 milliliters (mL) of blood from the volunteers. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn will be more than the amount indicated above.

Heart tracing
To make a heart tracing, electrodes will be placed on the arms, chest and legs.

In Group 1, heart rate will also be monitored continuously with telemetry for a longer period, for which electrodes will be placed on the chest and abdomen. Prolonged use of these electrodes can cause skin irritation.

Fasting
If the volunteer has to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

Coronavirus test
Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause the volunteer to gag. When the sample is taken from the back of the nose, the volunteer may experience a stinging sensation and the eyes may become watery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Sex assigned at birth : male or female; females of nonchildbearing potential, or postmenopausal.
2. Age : 18 to 65 years, inclusive, at screening.
3. Body mass index (BMI) : 18.0 to 32.0 kg/m2, inclusive, at screening.
4. Weight : >=50 kg.
5. Status : healthy subjects.

Exclusion criteria

1. Employee of PRA or the Sponsor.
2. History of relevant drug and/or food allergies.
3. History of alcohol abuse or drug addiction (including soft drugs like cannabis products) within 2 years prior to screening in the current study.
4. History or presence of atrioventricular block (any degree) or sick sinus syndrome.
5. Subjects with increased cardiac risk evaluation based on the following criteria:

• Smoking (no more than 2 packs of cigarettes) in the last 6 months prior to admission, including use of nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, e-cigarettes, or inhalers), or positive cotinine test at screening (ie, cotinine value >500 ng/mL will be excluded).
• Subjects with first-degree family history of ischemic cardiac event at a young age (male <55; female <65 years).
• Subjects with family history of arrhythmia, sudden unexplained death at a young age (before 40 years) in a first-degree relative, or long QT syndrome, Torsades de Pointes (TdP), or a personal history of repeated or frequent syncope or vasovagal episodes, or treatment for high blood pressure.
• History or presence of resuscitated arrest possibily due to TdP; hypertension, angina, or severe peripheral arterial circulatory disorders.
• History or presence of risk factors for TdP (eg, congenital deafness, heart failure, cardiomyopathy).
• History or presence of myocardial infarction, pulmonary congestion, cardiac arrhythmia, or prolonged QT interval, or conduction abnormalities.
• History or presence of concomitant medications-induced QTc prolongation within 30 days prior to screening.
• History or presence of hypokalemia, hypomagnesemia, or hypocalcemia.

See the protocol for the complete overview

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-09-2021
Enrollment:	48

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	fexofenadine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	quinidine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-003459-40-NL
CCMO	NL78420.056.21

Study results

Date completed: 27-12-2021

Results posted: 09-02-2023

First publication
24-01-2023